Spatial and temporal regulation of coronary vessel formation by calcineurin-NFAT signaling.

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Authors: Miriam Zeini, Calvin T Hang, Joshua Lehrer-Graiwer, Tiffany Dao, Bin Zhou, Ching-Pin Chang

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Public Summary:
This article describes how different signaling pathways (calcineurin-NFAT, VEGF) interacts in vascular progenitor cells to orchestrate the development of coronary vessels in the heart.

Scientific Abstract:
Formation of the coronary vasculature requires reciprocal signaling between endothelial, epicardially derived smooth muscle and underlying myocardial cells. Our studies show that calcineurin-NFAT signaling functions in endothelial cells within specific time windows to regulate coronary vessel development. Mouse embryos exposed to cyclosporin A (CsA), which inhibits calcineurin phosphatase activity, failed to develop normal coronary vasculature. To determine the cellular site at which calcineurin functions for coronary angiogenesis, we deleted calcineurin in endothelial, epicardial and myocardial cells. Disruption of calcineurin-NFAT signaling in endothelial cells resulted in the failure of coronary angiogenesis, recapitulating the coronary phenotype observed in CsA-treated embryos. By contrast, deletion of calcineurin in either epicardial or myocardial cells had no effect on coronary vasculature during early embryogenesis. To define the temporal requirement for NFAT signaling, we treated developing embryos with CsA at overlapping windows from E9.5 to E12.5 and examined coronary development at E12.5. These experiments demonstrated that calcineurin-NFAT signaling functions between E10.5 and E11.5 to regulate coronary angiogenesis. Consistent with these in vivo observations, endothelial cells exposed to CsA within specific time windows in tissue culture were unable to form tubular structures and their cellular responses to VEGF-A were blunted. Thus, our studies demonstrate specific temporal and spatial requirements of NFAT signaling for coronary vessel angiogenesis. These requirements are distinct from the roles of NFAT signaling in the angiogenesis of peripheral somatic vessels, providing an example of the environmental influence of different vascular beds on the in vivo endothelial responses to angiogenic stimuli.